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A MULTIPLE-DOSE PHARMACOKINETIC INTERACTION STUDY BETWEEN DIDANOSINE (VIDEX®) AND CIPROFLOXACIN (CIPRO®) IN MALE SUBJECTS SEROPOSITIVE FOR HIV BUT ASYMPTOMATIC

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ABSTRACT

The pharmacokinetics of didanosine and ciprofloxacin were evaluated following the administration of multiple oral doses of each drug as a single agent or in combination. Didanosine was dosed as the Videx® chewable/dispersible tablet, which contains the antacids dihydroxyaluminum sodium carbonate and magnesium hydroxide. Sixteen HIV-seropositive male subjects were randomly assigned to two groups of eight each. Group A received didanosine (200 mg q12h) for 3 d, followed by didanosine (200 mg q12h) and ciprofloxacin (750 mg q12h) for 3 d, and finished with another course of didanosine (200 mg q12h for 3 d). Group B began with ciprofloxacin, followed by the combination, and finished with ciprofloxacin using the same doses and schedule as utilized in group A. During the combination phase of the study, ciprofloxacin was administered 2 h prior to didanosine. Serial blood and urine samples were collected on study days 4, 8, and 12 for the quantitative determination of didanosine and ciprofloxacin using validated HPLC methods. The plasma and urine data were subjected to noncompartmental pharmacokinetic analysis. A statistically significant decrease in the average AUC and UR values of ciprofloxacin was noted when it was given with didanosine, relative to administration as a single agent. However, the magnitude of the decrease in these parameters, approximately 26 and 29%, respectively, was not considered clinically significant. The apparent decrease in the bioavailability of ciprofloxacin was probably due to the formation of a chelation complex between it and the aluminum- and magnesium-containing antacids found in the didanosine tablet. Other than an approximately 16% decrease in AUC, ciprofloxacin did not alter the pharmacokinetics of didanosine. The data from the present study demonstrate that didanosine or ciprofloxacin can be added to a treatment regimen consisting of the other single agent and that cessation of treatment with one agent does not have an impact on the pharmacokinetics of the other drug. The dose of ciprofloxacin must be taken at least 2 h prior to didanosine to avoid a clinically significant interaction with the antacids present in the didanosine formulation.

KEY WORDS: Videx; didanosine; ddI; ciprofloxacin; drug interaction

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INTRODUCTION

Didanosine (dideoxyinosine, ddI, Videx®) is a purine nucleoside analogue with *in vitro* activity against human immunodeficiency virus (HIV).[1] It is approved for the treatment of adult and pediatric subjects (over 6 months of age) when treatment with an antiretroviral agent is indicated.

The pharmacokinetics of didanosine have been extensively evaluated during the course of phase I safety and tolerance studies.[2,3] The kinetic profile is linear over a dose range of 0·4–16·5 mg kg^{-1} administered intravenously and 0·8–10·2 mg kg^{-1} orally and is invariant upon repeated dosing for as long as 4 weeks. The average renal clearance is 400 mL min^{-1}, a value that exceeds the glomerular filtration rate in man, indicating that active tubular secretion of didanosine occurs. The apparent elimination half-life after oral administration is 1·4 h. In order to protect didanosine from acid-induced hydrolysis in the stomach, it must be administered with an antacid.[4,5] Consequently, the formulations available for oral use contain excipients such as magnesium hydroxide, dihydroxyaluminum sodium carbonate, or a blend of citrate and phosphate buffer powders to increase the pH of the gastric environment.

Ciprofloxacin (Cipro®) is a fluoroquinolone antibiotic with a broad spectrum of activity against gram-positive and gram-negative organisms *in vitro*.[6] It is particularly useful in the treatment of respiratory and urinary tract infections due to multiple pathogens or pathogens resistant to other antibiotics.[6] Ciprofloxacin, when used in combination with antimycobacterial agents, may be active against disseminated *Mycobacterium avium*.[7,8] As a result of its broad spectrum of activity, ciprofloxacin may be frequently administered to patients with AIDS.

Fluoroquinolones, such as ciprofloxacin, have been shown to interfere with the *in vitro* and *in vivo* metabolism of methylxanthine derivatives such as caffeine and theophylline.[9–11] Structurally, methylxanthines are similar to the purine base of didanosine. Although some of the metabolic pathways impacted by ciprofloxacin are not relevant to didanosine, it has not been determined what effect ciprofloxacin may have on xanthine oxidase, a key enzyme in purine metabolism.

The absorption of ciprofloxacin is impaired when it is administered with magnesium- and aluminum-containing antacids,[12,13] although this effect can be minimized by administering ciprofloxacin 2 h prior to the antacid.[13] A previous study has demonstrated that coadministering placebo tablets of the didanosine formulation with ciprofloxacin results in 98% decrease in the bioavailability of the quinolone.[14]

Since didanosine and ciprofloxacin will be coadministered to patients with AIDS, it is necessary to assess whether there is a clinically significant interaction in their pharmacokinetics. The present study was designed to determine the steady-state pharmacokinetic profile of didanosine administered before, during, and after concomitant administration with ciprofloxacin, to

determine the steady-state pharmacokinetic profile of ciprofloxacin administered before, during, and after concomitant administration with didanosine, and to monitor subjects for safety.

MATERIALS AND METHODS

Subjects

Sixteen subjects seropositive for HIV who did not have clinical evidence of HIV-related disease were enrolled in this study. This population was selected to minimize the effect that concurrent disease conditions or concomitant medications may have had on the pharmacokinetics of didanosine and ciprofloxacin. Prior to the initiation of the study, the study protocol and informed consent form were approved by the local Institutional Review Board at the study site. Each subject gave written informed consent before any study-related procedures were conducted. The subjects were male and between 18 and 50 years of age, with stable health, normal vital signs, specified baseline laboratory values, and initial body weights between 60 and 100 kg and within $\pm 15\%$ of weight for height according to the Metropolitan Life Insurance Company standards. Subjects with a history of chronic organ dysfunction or any condition requiring regular or frequent treatment with drugs, recent diarrheal illness, or a history of pancreatitis were excluded from participation in the study. Subjects receiving prophylactic treatment with zidovudine were required to stop taking this medication 5 d prior to the first dose of the study and for the duration of the study. The subjects had a mean age of 33 years (range, 23–47 years), a mean weight of 75·2 kg (range, 64·5–89·3 kg), and a mean height of 176 cm (range, 165–185 cm). All the subjects were Caucasian.

Drug formulations

The study drugs, didanosine and ciprofloxacin, were packaged, labeled, and supplied to the investigator by the Bristol–Myers Squibb Company. Didanosine was supplied as the Videx® chewable/dispersible buffered tablet, containing 100 mg didanosine per tablet. Ciprofloxacin was supplied as a 750 mg strength capsule of Cipro®. The drug supplies were stored in a secure area at room temperature (59–86 °F, 15–30 °C) protected from moisture, freezing, and excessive heat.

Study design

This was a single-site, open, multiple-dose, study in which subjects were randomly assigned to two parallel groups of eight each. Group A received a course of didanosine (200 mg q12h for 3 d) followed by a course of didanosine

(200 mg q12h) and ciprofloxacin (750 mg q12h) for 3 d and finished with a final course of didanosine (200 mg q12h for 3 d). Subjects randomized to group B began with ciprofloxacin, followed by the combination, and finished with ciprofloxacin using the same doses and schedule as utilized in group A. Ciprofloxacin was administered 2 h prior to didanosine during the combination phases of the study. Pharmacokinetic evaluations were performed after the administration of the last dose of each course, given in the morning of study days 4, 8, and 12. On pharmacokinetic evaluation days, at least a 10 h fast was observed prior to dosing, and subjects were not allowed to eat until 4 h after dosing. Each dose of didanosine consisted of two tablets, which were chewed rapidly in succession, followed by a rinse with 120 mL water. One ciprofloxacin tablet was swallowed with 120 mL water. An additional 120 mL water was consumed 2 h after each single-agent dose.

The subjects were confined in the clinic beginning on the evening preceding days 4, 8, and 12 and released 24 h after dose administration. The subjects were contacted on a daily basis while outpatients to determine whether any adverse events were occurring. Safety assessments included the evaluation of vital signs for at least 1 h after dosing on study days 1, 4, 5, 8, and 12 and the determination of serum chemistry and hematology values prior to the first dose of the study and at the end of the study.

Sample collection and handling

Approximately 5 mL blood was collected using Becton–Dickinson Vacutainers®, which contain heparin as an anticoagulant. When didanosine and ciprofloxacin were coadministered, the volume of each blood sample was 10 mL. Serial samples were obtained at the following times after dosing: (i) didanosine, pre-dose (0 time), 15, 30, and 45 min and 1, 1·5, 2, 3, 4, 6, 8, and 12 h; (ii) ciprofloxacin, pre-dose (0 time), 15, and 30 min and 1, 1·5, 2, 4, 6, 8, 12, 16, and 24 h; and (iii) didanosine and ciprofloxacin, pre-dose (0 time), 15, and 30 min and 1, 1·5, 2, 2·25, 2·5, 2·75, 3, 3·5, 4, 5, 6, 8, 10, 12, 14, 16, and 24 h, where time 0 is the time of the ciprofloxacin dose. Immediately after collection, each blood sample was gently inverted and placed in chipped ice. The sample was centrifuged (within 1 h of collection) at 1000 *g* for 15 min at 5 °C. The plasma samples were collected and kept frozen at −20 °C until analysis.

Each urine sample collected during each interval consisted of the total urine voided over the specified collection interval. The subjects were instructed to void in a separate urine collection vessel for each interval and to keep that bottle refrigerated, except during voiding. The subjects were also instructed to void completely at the end of each collection period. At the end of each interval, the urine sample was mixed and the pH and total volume were recorded. A 2 mL aliquot was transferred to a screw-capped polypropylene tube containing 4 mL 0·2 M phosphate buffer (pH 8·0) for the analysis of didanosine. A separate 10 mL aliquot was transferred to another tube for the

analysis of ciprofloxacin. The samples were stored frozen at $-20\,^{\circ}C$ until analysis. Urine was collected at the following times after dosing: (i) didanosine, pre-dose, 0–4, 4–8, and 8–12 h; (ii) ciprofloxacin, pre-dose, 0–4, 4–8, 8–12, and 12–24 h; and (iii) didanosine and ciprofloxacin, pre-dose, 0–2, 2–6, 6–10, 10–14, and 14–24 h, where time 0 is the time of the ciprofloxacin dose.

Analyses of biological fluids

Analyses of didanosine in plasma and urine samples were carried out using an assay based upon a published high-performance liquid chromatographic (HPLC) assay procedure with ultraviolet detection.[15]

The concentrations of ciprofloxacin in plasma and urine were determined using a validated HPLC/fluorescence method adapted from a published procedure.[16] Briefly, ciprofloxacin and the internal standard norfloxacin were extracted from plasma or urine using 10% isopropranol in methylene chloride, followed by evaporation of the organic solvent. The residue was reconstituted in the mobile phase and a suitable aliquot was injected onto a Beckman Ultrasphere ODS column (25 cm × 4·6 mm I.D.). The mobile phase was 5% acetonitrile, 14% methanol in 26 mM monobasic potassium phosphate buffer containing 5 mM tetrabutylammonium bromide, pH 3·0, delivered at a flow rate of $1{\cdot}0\,mL\,min^{-1}$. The HPLC eluate was monitored using a fluorescence detector with excitation and emission settings of 270 and 440 nm, respectively.

Quality control samples containing didanosine or ciprofloxacin were prepared in each matrix at the time of study initiation and were analyzed along with the study samples in order to verify the stability of study samples during shipment and storage, and the assay accuracy and precision. Prior to the initiation of study sample analysis it was verified using spiked samples that the two drugs did not interfere with the accurate quantitation of each other. Data from standards, prepared in the appropriate biological fluid, were fit to a linear regression equation by weighting each standard by the reciprocal of its concentration and testing for outliers by the method of Prescott.[17] The concentration of didanosine or ciprofloxacin in each sample was derived by inverse prediction from the regression line. The ranges of the didanosine standard curves in plasma and urine were 25–10 000 $ng\,mL^{-1}$ and 1–400 $\mu\,mL^{-1}$, respectively. For ciprofloxacin, the standard curves ranged between 100 and 3000 $ng\,mL^{-1}$ in plasma and 0·25 to 25 $\mu g\,mL^{-1}$ in urine. The coefficients of determination for the standard curves, regardless of analyte or matrix, were consistently at least 0·996. The within- and between-day precision estimates for quality control sample concentrations distributed across the ranges of the standard curves were between 6 and 9% relative standard deviation (RSD). The average mean predicted concentrations for the quality control samples were within 4–11% of the nominal values. These data indicate that the assays for didanosine and ciprofloxacin in plasma and

urine were accurate and precise, in addition to demonstrating the stability of the analytes under the conditions used to store the study samples.

Pharmacokinetic analysis

The plasma concentration, C, versus time, t, data were analyzed by a noncompartmental method.[18,19] The terminal elimination rate constant, k_{el}, was derived from the absolute value of the terminal slope of the log-linear portion of the plasma profile. The log-linear phase was defined by a minimum of three of the last n data points (ln C, t), where n was selected to minimize the mean square error. The apparent elimination half-life, $t_{1/2}$, was calculated by dividing 0·693 by k_{el}. The area under the plasma concentration versus time curve over the dosing interval, AUC(TAU), was calculated using a combination of trapezoidal and log-trapezoidal methods.[19] In the case of didanosine, where measurable concentrations were not detectable in the plasma at the end of the dosing interval, the concentration at 12 h was predicted according to the equation $C_{12\,h} = B \exp(-\beta t)$ where B and β are, respectively, the regression (antilog) intercept and slope (absolute value) estimates from the linear, least-squares fit to the function, $\ln C = \ln B - \beta t$. Renal clearance, CL_r, was calculated by dividing the amount of didanosine or ciprofloxacin recovered in the urine in the 12 h interval after dosing by the AUC(TAU). The cumulative percent of dose recovered in the urine as unchanged didanosine or ciprofloxacin, UR, was calculated by dividing the amount excreted in the urine by the administered dose and multiplying by 100. The peak plasma concentration C_{max}, and the time to reach peak concentration, t_{max}, were recorded directly from the experimental observations.

Statistical analyses

Repeated-measures analysis was conducted for C_{max}, t_{max}, $t_{1/2}$, AUC(TAU), CL_r, and UR. For the didanosine group (A), the pharmacokinetics of didanosine were compared for the three pharmacokinetic sampling days (4, 8, and 12). For the ciprofloxacin group (B), the pharmacokinetics of ciprofloxacin were also compared for these three sampling days. The analysis of variance (ANOVA) specified effects for subject and sampling day.[20] In the case of t_{max}, its rank transformation was used to perform the analysis.[21] The subject and day effects were estimated using type III sums of squares. Significance of patient and day effects were determined using the mean square error term. If the effect of days was statistically significant, then Tukey's procedure was used to make pairwise comparisons based on the mean.[21] Box–Cox analysis was used to determine whether the analysis was performed on the raw or log-transformed data.[23] If the likelihood ratio test was significant, then the analysis based on the natural log transformation was reported. Levene's test was used to check the assumption of homogeneity of variance among sampling times.[24]

A two-sample *t*-statistic was used to compare the didanosine and ciprofloxacin groups with respect to the day 8 pharmacokinetics when both groups were receiving both drugs. If the groups were found to have unequal variances, the *t*-statistic and degrees of freedom were adjusted accordingly.[25]

All statistical calculations and tests were performed using the SAS package. The value $p = 0{\cdot}05$ was used as the significance level for all tests except Levene's test ($p = 0{\cdot}001$).

RESULTS

Pharmacokinetics of didanosine

The mean plasma concentration versus time profiles for didanosine are shown in Figure 1. The mean (SD) pharmacokinetic parameters are summarized in Table 1. For subjects in group A (assigned to receive didanosine), the Box–Cox analysis indicated that the natural log transform was appropriate for the parameters C_{max} and AUC(TAU). A statistically significant day effect was observed for C_{max} and AUC(TAU). For both parameters, the mean values measured during coadministration with ciprofloxacin (day 8) were significantly less than those observed when didanosine was administered as a single agent on day 12. The magnitude of the decrease was 33% for C_{max} and 21% for AUC. A decrease (23% for C_{max} and 11% for AUC) was also noted relative to day 4, but it was not statistically significant. No statistically significant pairwise differences among days were observed for t_{max}, $t_{1/2}$, CL_r, or UR. Comparison of didanosine pharmacokinetic parameters obtained on day 8 in groups A and B showed a nearly statistically significant difference between groups for AUC(TAU) ($p = 0{\cdot}0639$). The mean value for AUC(TAU) for the didanosine group was 1391 h ng mL^{-1}, as compared to the mean for the ciprofloxacin group of 1914 h ng mL^{-1}. There were no other statistically significant group differences between the day 8 pharmacokinetic parameters for didanosine.

Pharmacokinetics of ciprofloxacin

The mean plasma concentration versus time profiles for ciprofloxacin are shown in Figure 2. The individual and mean (SD) pharmacokinetic parameters obtained for ciprofloxacin are presented in Table 2. For subjects in group B (assigned to receive ciprofloxacin), the Box–Cox analysis indicated that the natural log transform was appropriate for UR. A statistically significant day effect was observed for AUC(TAU) and UR. For both parameters, the mean values obtained on day 8 during the combination phase of the study were significantly less than those observed when ciprofloxacin was administered as a single agent on days 4 and 12. The magnitude of the decrease was

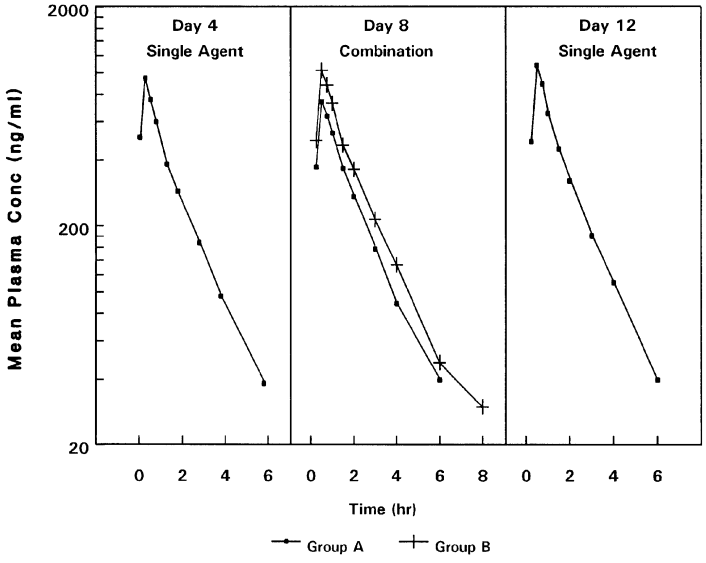

Figure 1. Mean steady-state plasma concentration–time profiles of didanosine administered as a single agent (200 mg q12h) or with ciprofloxacin (750 mg q12h)

approximately 26% for AUC and 29% for UR. C_{max} was also decreased by approximately 16%, although this change was not significant. No statistically significant pairwise differences among days were observed for t_{max}, $t_{1/2}$, or CL_r. There were no significant differences noted between groups A and B with respect to the pharmacokinetics of ciprofloxacin.

Table 1. Mean (SD) values for key pharmacokinetic parameters of didanosine administered as a 200 mg dose q12h either as a single agent (days 4 and 12) or 2 h after ciprofloxacin (750 mg q12h)

	Group A			Group B
Parameter	Day 4	Day 8	Day 12	Day 8
C_{max} (ng mL^{-1})	1016 (389)	781 (204)[a]	1162 (345)	1100 (531)
t_{max}[b] (h)	0·50 (0·50, 1·00)	0·50 (0·50, 1·00)	0·50 (0·50, 1·00)	0·63 (0·50, 1·00)
AUC(TAU) (h ng mL^{-1})	1568 (345)	1391 (433)[a]	1762 (394)	1914 (620)
$t_{1/2}$ (h)	1·26 (0·10)	1·29 (0·21)	1·33 (0·26)	1·42 (0·26)
CL_r (mL min^{-1})	336 (95)	348 (123)	355 (136)	301 (30)
UR (%)	15·2 (2·5)	13·6 (4·4)	18·5 (7·1)	17·2 (4·5)

[a]Significantly different from value on day 12.
[b]Median (minimum, maximum) values are reported.

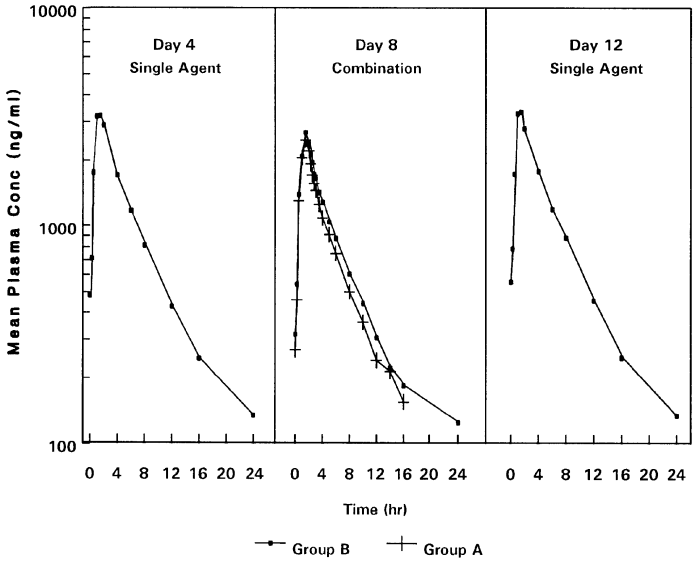

Figure 2. Mean steady-state plasma concentration–time profiles of ciprofloxacin administered as a single agent (750 mg q12h) or with didanosine (200 mg q12h)

Safety assessment

There were no clinically significant changes noted in vital signs after dosing relative to prior to dosing. Findings from the physical examination and clinical laboratory assessments pre- and post-study were comparable. A total of 23 adverse events of mild to moderate severity were noted, including nine episodes

Table 2. Mean (SD) values for key pharmacokinetic parameters of ciprofloxacin administered as a 750 mg dose q12h either as a single agent (days 4 and 12) or 2 h before didanosine (200 mg q12h)

	Group B			Group A
Parameter	Day 4	Day 8	Day 12	Day 8
C_{max} (ng mL^{-1})	3644 (773)	2996 (791)	3469 (621)	2654 (555)
t_{max}[a] (h)	1·25 (1·00, 2·00)	1·50 (0·50, 2·25)	1·25 (1·00, 1·50)	1·25 (0·50, 2·00)
AUC(TAU) (h ng mL^{-1})	16 743 (3649)	12 557 (3440)[b]	17 169 (2978)	11 098 (3009)
$t_{1/2}$ (h)	5·26 (1·29)	5·31 (1·51)	5·70 (1·45)	4·42 (0·82)
CL_r (mL min^{-1})	195 (48)	200 (62)	207 (49)	222 (65)
UR (%)	29·9 (9·4)	22·2 (4·5)[b]	32·4 (9·2)	21·4 (1·8)

[a]Median (minimum, maximum) values are reported.
[b]Significantly different from values on days 4 and 12.

of headache; two episodes each of nausea, cough, throat pain, and rhinitis; and one episode each of chills, fever, increased energy, diarrhea, dyspepsia, and dizziness. The relationship of any of these adverse events to the administration of either didanosine or ciprofloxacin was not known. All events were resolved prior to the completion of the study.

DISCUSSION

The data from this study demonstrated that there was a modest decrease in the bioavailability of ciprofloxacin when it was administered 2 h prior to a dose of the didanosine chewable tablet formulation. However, trough concentrations remained above the MIC_{90} values for many pathogens considered susceptible to ciprofloxacin,[6] suggesting that the activity of the antibiotic should not be altered. It has been shown previously that concurrent administration of ciprofloxacin with two didanosine placebo tablets results in a 98% decrease in the average AUC value of ciprofloxacin.[14] Ciprofloxacin, and other fluoroquinolones such as temafloxacin,[26] lomefloxacin,[27] and ofloxacin,[28] are believed to form insoluble chelation complexes with divalent and trivalent cations such as magnesium and aluminum, respectively. There is also indirect evidence that complexation occurs between ciprofloxacin and calcium.[12,28] The net result is that the chelated quinolone is no longer available for absorption, resulting in decreased bioavailability. The chewable tablet formulation of didanosine is comprised of both aluminum- and magnesium-containing antacids. Other didanosine formulations, such as the pediatric powder for oral solution (which is mixed with Maalox®) and the reduced mass tablet (which contains magnesium hydroxide and calcium carbonate), would also be expected to cause a decrease in the bioavailability of ciprofloxacin if ingested at the same time. The buffered powder for oral solution product, however, may not alter the absorption of ciprofloxacin since it relies on dibasic sodium phosphate and sodium citrate to alter the pH environment of the stomach rather than on metallic antacids. It has already been shown that the decrease in the bioavailability of ciprofloxacin is not a result of an increase in gastric pH, since pretreatment with ranitidine did not have an effect on the C_{max} or AUC values of ciprofloxacin.[13] The impact of the interaction between ciprofloxacin and the metallic cations can be minimized by administering ciprofloxacin either 2 h before or 6 h after an antacid.[13] The data from the present study suggest that a similar strategy should be used in subjects requiring concomitant therapy with a fluoroquinolone and didanosine.

The administration of multiple concurrent doses of didanosine did not have any effect on other pharmacokinetic parameters of ciprofloxacin, such as t_{max} or $t_{1/2}$. Despite the fact that both ciprofloxacin and didanosine undergo active renal tubular secretion,[2,6] there were no apparent changes in the renal clearance of either drug, suggesting that competition for the carrier system(s) did not

occur. Ciprofloxacin C_{max}, AUC, $t_{1/2}$, and UR values obtained on day 4 are in reasonable agreement with data reported by Gonzalez *et al.*, after the administration of a similar number of the same dose.[29]

The pharmacokinetics of didanosine were not altered when it was given with ciprofloxacin. Although there was a minor apparent decrease in the AUC of didanosine in the subjects assigned to group A during coadministration, relative to when ciprofloxacin was withdrawn, this appeared to be the result of intrasubject variability since there was no difference relative to the AUC value obtained for didanosine as a single agent before ciprofloxacin was introduced. In group B, the didanosine AUC was actually greater, by approximately 15%, during the coadministration phase, relative to the average on days 4 and 12 for group A. The apparent lack of change in the elimination characteristics of didanosine when it was administered with ciprofloxacin suggests that the metabolism of didanosine was not impacted. Ciprofloxacin has been shown to inhibit the microsomal N-demethylation of methylxanthines such as theophylline and caffeine, leading to an increase in $t_{1/2}$ and AUC and a decrease in clearance in subjects receiving both agents.[9–11,30] Studies conducted *in vitro* have not been able to assess the impact of ciprofloxacin on the xanthine-oxidase-catalyzed oxidation of 1-methylxanthine (1-MX), a key metabolite of theophylline, since xanthine oxidase is a cytosolic enzyme and therefore not present in a microsomal fraction. A decrease in the urinary recovery of 1-methyluric acid (1-MU), formed from 1-methylxanthine through the action of xanthine oxidase, was noted when theophylline was administered with another fluoroquinolone, enoxacin.[9] It is likely, however, that the decrease in 1-MU excretion is due to the decreased amount of 1-MX rather than due to an effect of the quinolone on xanthine oxidase directly. Even if xanthine oxidase activity were affected by ciprofloxacin, there probably would be no effect on the pharmacokinetics of didanosine, since the putative first step in its metabolism involves the hydrolysis of the dideoxyribose–purine base linkage by purine nucleoside phosphorylase.

The data from the present study demonstrated that either didanosine or ciprofloxacin could be added to a treatment regimen consisting of the other single agent without altering the pharmacokinetics of either drug to a degree that was clinically significant. Cessation of treatment with one agent also did not have any discernible impact on the pharmacokinetics of the other. It is concluded that didanosine and ciprofloxacin may be safely coadministered without adjusting the dosing regimen of either compound, so long as the dose of ciprofloxacin is taken at least 2 h before didanosine.

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